



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(54) Title: RHODANINE CARBOXYLIC ACID DERIVATIVES FOR THE TREATMENT AND PREVENTION OF METABOLIC BONE DISORDERS</p> <div style="text-align: center; margin: 20px 0;"> </div> <p style="text-align: right; margin-right: 50px;">(I)</p>		
<p>(57) Abstract</p> <p>The object of the present invention are compounds of general formula (I), in which m signifies a number between 0-8, q signifies a number between 0-8, a signifies a number between 0-4, A signifies a single or double bond, R<sub>1</sub>, R<sub>2</sub> signify hydrogen or lower alkyl, whereby R<sub>1</sub> and R<sub>2</sub> can be the same or different and, when m signifies 2-8, R<sub>1</sub> and R<sub>2</sub> in the group CR<sub>1</sub>=CR<sub>2</sub> can have various significances within the following sequence, R<sub>3</sub> signifies hydrogen or lower alkyl, X signifies hydrogen or -(CH<sub>2</sub>)<sub>b</sub>-COR<sub>4</sub> with b=0-4, Y signifies hydrogen, -COR<sub>4</sub>, phenyl or indolyl residue R<sub>4</sub> signifies hydroxyl, lower alkoxy or the NR<sub>1</sub>R<sub>2</sub> residue, whereby R<sub>1</sub> and R<sub>2</sub> can be the same or different, W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms, as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers as well as derivatives which can be metabolized <i>in vivo</i> to compounds of general formula (I), as well as the use of these compounds for the production of medicaments for the prophylaxis or therapy of metabolic bone disorders.</p>		

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5 **Rhodanine carboxylic acid derivatives for the treatment and prevention of metabolic bone disorders**

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10 The present invention is concerned with rhodanine carboxylic acid derivatives for the treatment and prevention of metabolic bone disorders, a process for their manufacture as well as medicaments which contain these compounds.

15 In healthy persons the synthesis and degradation processes in bones is almost in equilibrium, i.e. the activity of the osteoblasts and osteoclasts is balanced. However, if this equilibrium is disturbed in favour of the osteoclasts and/or to the detriment of the osteoblasts, this leads to a reduction in the bone mass and to a negative change in the bone structure and function.

20 Hitherto, bone resorption inhibitors such as oestrogens, calcitonin and biphosphonates have primarily been used for the treatment of metabolic bone disorders. The use of these substances is, however, limited and also does not show the desired effect in all cases. Compounds which have a stimulating activity on bone synthesis and in addition contribute to an increase in an already reduced bone mass are accordingly of especial significance for the treatment of metabolic bone disorders.

25 Compounds having the rhodanine carboxylic acid structural element are known as antidiabetics, cytostatics inflammation inhibitors and for the treatment of cardiovascular illnesses and bacterial infections

30 The parathyroid hormone (PTH), a hormone from the parathyroid gland, is the natural ligand of the receptor and an important regulator for the maintenance of the calcium level in the body. PTH can stimulate bone formation or bone resorption. In this, it acts as a regulatory hormone on a series of enzymes, inter alia, on adenylate cyclase (cAMP synthesis) and on ornithine decarboxylase. PTH mobilizes calcium from bones in the case of calcium deficiency, reduces calcium excretion from the kidneys and  
35 simultaneously improves the resorption of calcium from the intestine by an increased

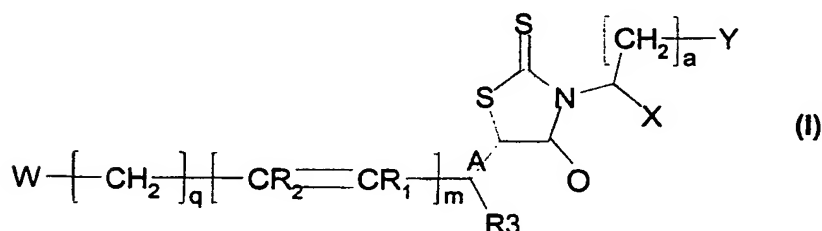
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synthesis of  $1,25-(\text{OH})_2\text{D}_3$ . A normalization of the calcium level is achieved by the action on these target organs. On the other hand, the incorporation of calcium in bones is stimulated in the case of an elevated calcium level. This osteoanabolic activity of PTH and its fragments has been attributed to the activation of adenylate cyclase and of cAMP-dependent protein kinases (Rixon, R. Whitfield, J. et al JMBR 9 (8) 1179-89 (1994)).

Surprisingly, it has now been found that rhodanine carboxylic acid derivatives of the present invention stimulate the PTH receptor-mediated cAMP formation. Compounds of the present invention are accordingly suitable for the broad treatment of metabolic bone disorders. They can be used primarily to good effect where the bone synthesis is disturbed, i.e. they are especially suitable for the treatment of osteopenic disorders of the skeletal system such as e.g. osteoporosis, inter alia, osteogenesis imperfecta as well as for the local assistance in bone regeneration and osteoinduction such as e.g. in orthopedic and maxillary medical indications, in fracture healing, osteosyntheses, pseudoarthroses and for the healing in of bone implants. However, having regard to these properties they also find use in the prophylaxis of osteoporosis.

By their influence on bone metabolism medicaments with the rhodanine carboxylic acid derivatives of the present invention as active substances furthermore form a basis for the local and systemic treatment of rheumatoid arthritis, osteoarthritis and degenerative arthrosis.

The object of the present invention are compounds of general formula (I),



in which

m signifies a number between 0-8,

q signifies a number between 0-8

a signifies a number between 0-4

A signifies a single or double bond

R<sub>1</sub>, R<sub>2</sub> signify hydrogen or lower alkyl, whereby

5 R<sub>1</sub> and R<sub>2</sub> can be the same or different and, when m signifies 2-8, R<sub>1</sub> and R<sub>2</sub> in the group CR<sub>1</sub>=CR<sub>2</sub> can have various significances within the following sequence

R<sub>3</sub> signifies hydrogen or lower alkyl

X signifies hydrogen or -(CH<sub>2</sub>)<sub>b</sub>-COR<sub>4</sub> with b = 0-4

10 Y signifies hydrogen, -COR<sub>4</sub>, phenyl or indolyl residue

R<sub>4</sub> signifies hydroxyl, lower alkoxy or the NR<sub>1</sub>R<sub>2</sub> residue, whereby R<sub>1</sub> and R<sub>2</sub> can be the same or different

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

15

As a rule, lower alkyl signifies linear or branched alkyl residues with one to six carbon atoms, preferably methyl, ethyl, propyl, i-propyl, butyl, t-butyl, pentyl, hexyl, particularly methyl.

20 Alkoxy groups signify a combination of a C<sub>1</sub>-C<sub>10</sub>-alkyl group in accordance with the above definition with an oxygen atom, e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentoxy groups.

Under monocycle there are to be understood optionally mono- or polysubstituted,  
 25 saturated or unsaturated ring systems with 3-8, preferably 5-7 carbon atoms, which optionally can be interrupted by one or more hetero atoms, such as nitrogen, oxygen or sulphur, especially the phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, morpholinyl, thiamorpholinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, furyl, thiophenyl, imidazolyl,  
 30 thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl residue, as well as residues such as e.g. phenyl phenyl ether, diphenylmethane and biphenyl. Substituents are preferably lower alkyl, alkoxy, alkoxycarbonylalkyl, alkoxycarbonyl, acetylamino, alkoxydialkylamino, amino, dialkylamino, benzyl, benzyloxy, benzyloxybenzyloxy, carboxyl, chlorophenylsulphanyl, dioxymethylene, mercaptoalkyl,  
 35 nitro, phenoxy, styryl and halogen.

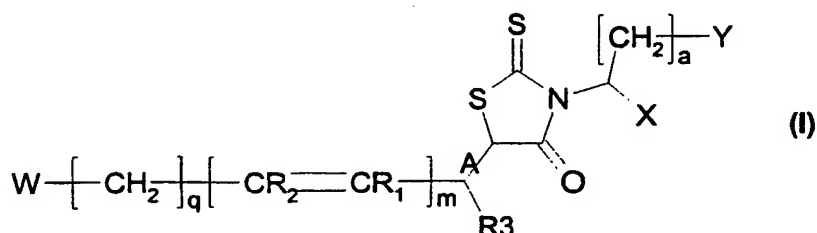
In the case of the bicycle set forth under W, this is preferably a residue such as the naphthyl, tetrahydronaphthyl, decaliny, quinoliny, chromane, chromene, isoquinoliny, tetrahydroquinoliny, tetrahydroisoquinoliny, indolyl, benzimidazolyl, indazolyl, oxindolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxazolyl or puriny residue, especially the indolyl, naphthyl, benzimidazolyl, quinoliny, tetrahydroquinoliny benzothiophenyl and benzofuranyl residue, which optionally can be mono- or polysubstituted. Substituents are preferably lower alkyl, alkoxy, alkoxycarbonylalkyl, alkoxycarbonyl, acetylamino, alkoxydialkylamino, amino, dialkylamino, benzyl, benzyloxy, benzyloxybenzyloxy, carboxyl, chlorophenylsulphanyl, dioxymethylene, mercaptoalkyl, nitro, phenoxy, styryl and halogen.

In the case of the tricycle set forth under W, this is preferably a residue such as the anthracene, fluorene, dibenzofuran or carbazole.

15

Compounds of formula I wherein W is phenyl or indolyl, m and g are both 0, R<sub>3</sub> is hydrogen and A is a double bond are disclosed e.g. in EP-A-0677 and EP-A-0587377, however for the treatment of Alzheimer's disease or as hypoglycemic agents.

Therefore subject of the present invention are also new compounds of formula I



5

in which

m signifies a number between 0-8,

q signifies a number between 0-8

10 a signifies a number between 0-4

A signifies a single or double bond

**R<sub>1</sub>, R<sub>2</sub> signify hydrogen or lower alkyl, whereby**

$R_1$  and  $R_2$  can be the same or different and, when  $m$  signifies 2-8,  $R_1$  and  $R_2$

in the group  $CR_1=CR_2$  can have various significances within the following

15                    sequence

R<sub>3</sub> signifies hydrogen or lower alkyl

X signifies hydrogen or  $-(CH_2)_b-COR_4$  with  $b = 0-4$

Y signifies hydrogen, -COR<sub>4</sub>, phenyl or indolyl residue

$R_4$  signifies hydroxyl, lower alkoxy or the  $NR_1R_2$  residue, whereby  $R_1$  and  $R_2$  can

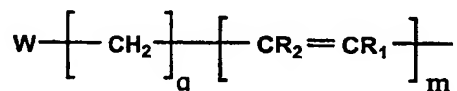
20            be the same or different

**W** signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

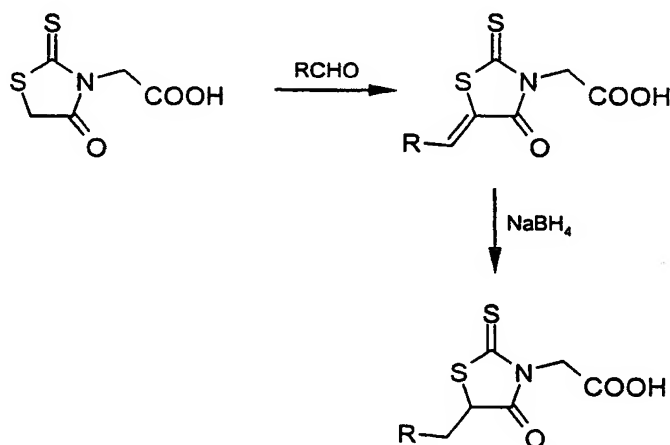
whereas W is not phenyl or indolyl, if m and g are both 0, R<sub>3</sub> is hydrogen and A is a double bond, as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments.

Preferred are compounds of general formula I in which m signifies a number between 0 and 4, q signifies the number 0 or 1, a signifies a number of 0 to 4, A signifies a double bond, R<sub>1,2</sub> signify hydrogen or methyl, X signifies hydrogen or -(CH<sub>2</sub>)<sub>b</sub>-COR<sub>4</sub> with b = 0-2 and R<sub>4</sub> equals hydroxyl, methoxy or NR<sub>1</sub>R<sub>2</sub>, Y signifies hydrogen or COR<sub>4</sub>, the phenyl or indolyl residue, R<sub>3</sub> signifies hydrogen or methyl and W signifies an optionally mono- or polysubstituted benzothiophene, phenyl, benzofuran, thiophene, naphthalene, piperidine, cyclohexenyl or biphenyl residue.

The manufacture of the compounds of general formula (I) is possible according to methods known per se. Examples of the methods of synthesis are set forth in Schemes 1 and 2; whereby R signifies the group:

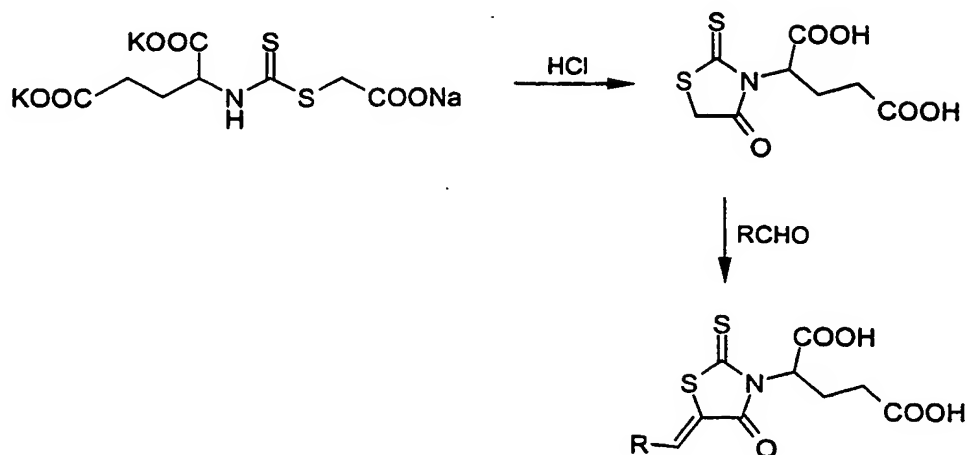


Scheme 1 (Lit.: Chem. Pharm. Bull. 38 1911-19 (1990); 40 907-11 (1992))





Scheme 2 (Lit.: Chem. Heterocycl. Compd. EN 3 528-30 (1967))



The rhodanine carboxylic acids and aldehydes used as starting materials are either commercially available, known or can be prepared analogously to the generally known processes.

Compounds of formula (I) can be administered (sic) in liquid, solid or aerosol form orally, enterally, parenterally, topically, nasally, pulmonary or rectally in all usual non-toxic pharmaceutically acceptable carrier materials, adjuvants and additives. The compounds of formula (I) can also be applied locally to/in the bones (optionally with surgical intervention). The term parenteral embraces subcutaneous, intravenous and intramuscular delivery or infusions. Oral administration forms can be e.g. tablets, capsules, dragees, syrups, solutions, suspensions, emulsions, elixirs etc., which can contain one or more additives from the following groups, such as flavourings, sweeteners, colouring agents and preservatives. Oral administration forms contain the active ingredient together with non-toxic, pharmaceutically acceptable carrier materials which are suitable for the production of tablets, capsules, dragees etc., such as e.g. calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; starch, mannitol, methylcellulose, talc, highly dispersible silicic acids, high molecular fatty acids (such as stearic acid), groundnut oil, olive oil, paraffin, miglyol, gelatine, agar-agar, magnesium stearate, beeswax, cetyl alcohol, lecithin, glycerol, animal and vegetable fats, solid high molecular polymers (such as polyethylene glycol). Tablets,

capsules, dragees etc. can be provided with an appropriate coating, e.g. glyceryl mono-stearate or glyceryl distearate, in order to prevent undesired side effects in the gastrointestinal tract or to give a longer duration of action by the delayed absorption in the gastrointestinal tract. As the injection medium there are preferably used sterile  
5 injectable aqueous or oily solutions or suspensions which contain the usual additives such as stabilizers and solubilizers. Such additives can be e.g. water, isotonic saline, 1,3-butanediol, fatty acids (such as oleic acid), mono- and diglycerides or miglyol. For rectal use there can be used all suitable non-irritating additives which are solid at normal temperatures and liquid at rectal temperatures, such as e.g. cocoa butter and  
10 polyethylene glycol. Pharmaceutically usual carrier media are used for application as aerosols. Creams, tinctures, gels, solutions or suspensions etc. with the pharmaceutically usual additives are used for external application. The dosage can depend on a variety of factors such as mode of administration, species, age and/or individual condition. The doses to be administered daily or at intervals lie at 1-  
15 1000 mg/individual, preferably at 10-250 mg/individual, and can be taken at one time or divided over several times.

The compounds of formula (I) can also be applied locally to/in the bones (optionally with surgical intervention). The application directly to/in the bones (optionally with  
20 surgical intervention) can be effected locally or carrier-bonded either in solution or suspension, conveniently by infusion or injection. Carrier-bonded compounds of formula (I) can be administered, for example, as gels, pastes, solids or as a coating on implants.

25 Biocompatible and preferably biodegradable materials are used as the carrier. Preferably, the materials themselves also induce wound healing or osteogenesis.

For local application it is preferred that the compounds of formula (I) are imbedded in polymer gels or films in order to immobilize them and to apply these preparations  
30 directly on the site of the bone to be treated. Such polymer-based gels or films consist, for example, of glycerine, methylcellulose, hyaluronic acid, polyethylene oxides and/or poloxamers. Also suitable are collagen, gelatines and alginates and are described, for example, in WO 93/00050 and WO 93/20859. Further polymers are polylactic acid (PLA) and copolymers of lactic acid and glycolic acid (PLPG) (Hollinger et al., J.  
35 Biomed. Mater. Res. 17 71-82 (1983)) as well as the bone derivative "Demineralized

Bone Matrix" (DBM) (Guterman et al. Kollagen Rel. Res. 8 419-4319 (1988). Also suitable are polymers as are used, for example, for the adsorption of TGF $\beta$  and which are described in EP-A 0 616 814 and EP-A-0 567 391 and synthetic bone matrices in accordance with WO 91/18558.

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Likewise suitable as carriers for the compounds of formula (I) are materials which are usually used for the implantation of bone substitutes or otherwise of therapeutically active substances. Such carriers are based, for example, on calcium sulphate, tricalcium phosphate, hydroxylapatite (sic) and its biodegradable derivatives and polyanhydrides.

10

Apart from these biodegradable carriers there are also suitable carriers which are not biodegradable, but which are biocompatible. Such carriers are, for example, sintered hydroxylapatite, bioglass, aluminates or other ceramic materials (e.g. calcium aluminium phosphate). These materials are preferably used in combination with the biodegradable materials, such as especially polylactic acid, hydroxylapatite, collagen or

15

tricalcium phosphate. Further non-degradable carriers are described, for example, in US Patent 4,164,560.

It is especially preferred to use a carrier which liberates the compounds of formula (I) continuously at the target site. Especially suitable for this are e.g. "slow release pellets" from Innovative Research of America, Toledo, Ohio, USA. Pellets which release the compounds of formula (I) over several days, preferably up to 100 days with a daily dosage of 1-10 mg/kg per day, are especially preferred.

20

Preferred in the scope of the present invention are, apart from the compounds named in the Examples and compounds derivable by a combination of all of the significances of the substituents set forth in the claims, the following derivatives as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments,

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#### Preferred Compounds (PC):

1. [5-(9H-Fluoren-2-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
2. (4-Oxo-5-phenanthren-9-ylmethyl-2-thioxo-thiazolidin-3-yl)-acetic acid
- 35 3. [5-(3-Anthracen-9-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid

4. 3-[5-(10-Methyl-anthracen-9-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
5. 3-[5-(5-Furan-2-yl-penta-2,4-dienylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
- 5 6. 2-(5-Benzylidene-4-oxo-2-thioxo-thiazolidin-3-yl)-succinic acid
7. 2-[5-(2-Methoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
8. [4-Oxo-2-thioxo-5-(2,3,4-trimethoxy-benzyl)-thiazolidin-3-yl]-acetic acid
9. {5-[3-(2,4-Dimethoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 10 10. 3-[4-Oxo-2-thioxo-5-(2,4,5-trimethoxy-benzylidene)-thiazolidin-3-yl]-propionic acid
11. 3-{4-Oxo-2-thioxo-5-[3-(2,4,6-trimethoxy-phenyl)-allylidene]-thiazolidin-3-yl}-propionic acid
- 15 12. 2-[5-(2,5-Dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
13. 2-[5-(2-Ethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
14. [5-(2-Hydroxy-3-methoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
- 20 15. {5-[3-(3-Ethoxy-2-hydroxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
16. 3-[5-(2,3-Dihydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
17. 3-{4-Oxo-2-thioxo-5-[3-(2,3,4-trihydroxy-phenyl)-allylidene]-thiazolidin-3-yl}-propionic acid
- 25 18. 2-[5-(4-Diethylamino-2-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
19. 2-[5-(2-Hydroxy-4-methoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
- 30 20. [5-(2-Hydroxy-5-methoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
21. {5-[3-(2,5-Dihydroxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
22. 3-[5-(2-Methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
23. 3-{5-[3-(4-Methoxy-2,3-dimethyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 35

24. 2-[4-Oxo-2-thioxo-5-(2,4,6-trimethyl-benzylidene)-thiazolidin-3-yl]-succinic acid
25. 2-[5-(2,5-Dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
- 5 26. {5-[3-(4-Methoxy-phenoxy)-benzyl]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
27. (5-{3-[3-(4-*tert*-Butyl-phenoxy)-phenyl]-allylidene}-4-oxo-2-thioxo-thiazolidin-3-yl)-acetic acid
28. 3-[4-Oxo-2-thioxo-5-(3-*p*-tolxyloxy-benzylidene)-thiazolidin-3-yl]-propionic acid
- 10 29. 3-{5-[3-(3-Methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
30. 2-[5-(3,4-Dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 15 31. 2-[4-Oxo-2-thioxo-5-(3,4,5-trimethoxy-benzylidene)-thiazolidin-3-yl]-pentanedicarboxylic acid
32. [5-(3,5-Dimethoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
33. {5-[3-(3-Benzyloxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 20 34. 3-[5-(3-Hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
35. 3-{5-[3-(3-Hydroxy-4-methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
36. 2-[5-(3,4-Dihydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 25 37. 2-[5-(3-Methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
38. [5-(4-Dimethylamino-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
39. {5-[3-(4-Diethylamino-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 30 40. 3-[4-Oxo-5-(4-phenoxy-benzylidene)-2-thioxo-thiazolidin-3-yl]-propionic acid
41. 3-{5-[3-(4-Methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
42. 2-[5-(3-Benzyloxy-4-methoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid

43. 2-[5-(4-Benzoyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
44. [5-(4-Butoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
45. [5-(3-Naphthalen-1-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
- 5 46. 3-[5-(2-Methoxy-naphthalen-1-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
47. 3-{5-[3-(2-Hydroxy-naphthalen-1-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
48. 2-[5-(4-Methoxy-naphthalen-1-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 10 49. 2-(5-Naphthalen-2-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-pentane-dicarboxylic acid
50. [5-(9-Ethyl-9*H*-carbazol-3-ylmethyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
- 15 51. {5-[3-(1*H*-Indol-3-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
52. 3-[5-(5-Methoxy-1*H*-indol-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
53. 3-[5-(3-Benzo[1,3]dioxol-5-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
- 20 54. 2-[5-(4-Hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
55. [5-(4-Hydroxy-3,5-dimethoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
56. {5-[3-(3-Ethoxy-4-hydroxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 25 57. 3-[5-(4-Hydroxy-3,5-dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
58. 3-[5-(3-Biphenyl-4-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
- 30 59. 2-[5-(4-Isopropyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
60. [5-(4-Ethyl-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
61. [5-(4,4-Diphenyl-but-2-enylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
62. 3-[4-Oxo-5-(2-phenyl-propylidene)-2-thioxo-thiazolidin-3-yl]-propionic acid

63. 3-[5-(4-Methyl-5-phenyl-penta-2,4-dienylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
64. 2-[5-(2-Hexyl-3-phenyl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
- 5 65. [4-Oxo-5-(5-phenyl-penta-2,4-dienylidene)-2-thioxo-thiazolidin-3-yl]-acetic acid
66. 3-{5-[3-(2-Methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
67. 3-{5-[5-(4-Dimethylamino-phenyl)-penta-2,4-dienylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 10 68. [5-(3-Ethoxy-4-methoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
69. {5-[3-(4-Diethoxymethyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
70. 3-[5-(4-Dimethylamino-naphthalen-1-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
- 15 71. 2-[5-(2,4-Dimethoxy-3-methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
72. [4-Oxo-5-(4-styryl-benzylidene)-2-thioxo-thiazolidin-3-yl]-acetic acid
73. {5-[4-(3-Dimethylamino-propoxy)-benzyl]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 20 74. {5-[3-(2,4-Dihydroxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
75. 3-[5-(2-Methyl-1*H*-indol-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
- 25 76. 3-{5-[3-(4-Hydroxy-3-methyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
77. 2-[5-(2-Hexyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
78. [4-Oxo-5-(4-propoxy-benzyl)-2-thioxo-thiazolidin-3-yl]-acetic acid
- 30 79. {4-Oxo-5-[3-(4-pentyloxy-phenyl)-allylidene]-2-thioxo-thiazolidin-3-yl}-acetic acid
80. 3-[5-(4-Octyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
81. 3-{5-[3-(5-Benzoyloxy-1*H*-indol-3-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid

82. 2-(5-Benzofuran-2-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-pentane-dicarboxylic acid
83. [4-Oxo-5-(2,3,4,5,6-pentamethyl-benzyl)-2-thioxo-thiazolidin-3-yl]-acetic acid
84. {5-[3-(2-Benzoyloxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 5 85. 3-[4-Oxo-2-thioxo-5-(2,3,4-trimethoxy-6-methyl-benzylidene)-thiazolidin-3-yl]-propionic acid
86. 3-{5-[3-(3-Ethoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 10 87. 2-[5-(3,4-Dihydroxy-5-methoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
88. [5-(3,4-Dimethyl-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
89. {5-[3-(4-Ethoxy-3-methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 15 90. 3-[5-(4-Hexyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
91. 3-{5-[3-(4-Heptyloxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
92. 2-(5-Benzo[1,3]dioxol-4-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-pentanedicarboxylic acid
- 20 93. [4-Oxo-2-thioxo-5-(2,4,5-trimethyl-benzyl)-thiazolidin-3-yl]-acetic acid
94. {5-[3-(4-Decyloxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
95. 3-{5-[3-(4-*tert*-Butyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 25 96. {5-[3-(4-Amino-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
97. 3-[5-(2-*tert*-Butylsulphanyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
98. 3-{5-[3-(4-Butyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 30 99. 2-[5-(4-*tert*-Butoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
100. [4-Oxo-5-(4-propyl-benzylidene)-2-thioxo-thiazolidin-3-yl]-acetic acid
101. [5-(4-Hexyl-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
- 35 102. {5-[3-(4-Octyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid



103. 3-[5-(4-Dodecyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
104. 3-{4-Oxo-5-[3-(4-pentyl-phenyl)-allylidene]-2-thioxo-thiazolidin-3-yl}-propionic acid
- 5 105. 2-[5-(3-Amino-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
106. [5-(7-Methyl-1*H*-indol-3-ylmethyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
107. 3-[4-Oxo-2-thioxo-5-(2-*p*-tolyl-ethylidene)-thiazolidin-3-yl]-propionic acid
- 10 108. 3-{5-[3-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
109. [5-(4-Hydroxy-2-methoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
110. {5-[3-(2,2-Dimethyl-chroman-6-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 15 111. 3-[5-(4-Isopropoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
112. 2-[5-(4-Methyl-naphthalen-1-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
113. {5-[3-(2,3-Dihydro-benzofuran-5-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 20 114. 3-(4-Oxo-5-quinolin-2-ylmethylene-2-thioxo-thiazolidin-3-yl)-propionic acid
115. 3-{5-[5-(4-Diethylamino-phenyl)-penta-2,4-dienylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
116. 2-[5-(4-Isobutyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentane-dicarboxylic acid
- 25 117. [5-(6-Methoxy-naphthalen-2-ylmethyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
118. {5-[3-(3,5-Dimethyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 30 119. 3-[5-(1-Hydroxy-naphthalen-2-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
120. [5-(4-Octadecyloxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
121. {5-[3-(4-Diphenylamino-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid

122. 3-[4-Oxo-2-thioxo-5-(3,4,5-trihydroxy-benzylidene)-thiazolidin-3-yl]-propionic acid
123. 3-{5-[3-(4-Dimethylamino-2-methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 5 124. {5-[2-(2-Hydroxy-ethoxy)-benzyl]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
125. (5-{3-[4-(2-Hydroxy-ethoxy)-phenyl]-allylidene}-4-oxo-2-thioxo-thiazolidin-3-yl)-acetic acid
126. 3-[5-(2-Benzylloxy-ethylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
127. 3-{5-[3-(4-*tert*-Butoxycarbonyloxy-3-methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 10 128. 2-[5-(2,4-Diethoxy-3-methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
129. [5-(2-Benzylloxy-3-methoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
- 15 130. {5-[3-(4-Methanesulphonyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
131. 3-[5-(2-Hydroxy-5-methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
132. (4-Oxo-5-thiophen-2-ylmethyl-2-thioxo-thiazolidin-3-yl)-acetic acid
- 20 133. [5-(5-Naphthalen-2-yl-penta-2,4-dienylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
134. 3-[4-Oxo-5-(3-thiophen-2-yl-allylidene)-2-thioxo-thiazolidin-3-yl]-propionic acid
135. 3-{5-[3-(2-[1,3]Dioxolan-2-yl-6-fluoro-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 25 136. 2-[5-(3-*tert*-Butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
137. [5-(4-Benzyl-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
138. {5-[5,9-Dimethyl-11-(2,6,6-trimethyl-cyclohex-1-enyl)-undeca-2,4,6,8,10-pentaenylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
- 30 139. 3-[4-Oxo-5-(1*H*-pyrrol-2-ylmethylene)-2-thioxo-thiazolidin-3-yl]-propionic acid
140. 3-[5-(3-Furan-2-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
141. 2-{5-[3-(5,6-Diethoxy-benzo[*b*]thiophen-2-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-pentanedicarboxylic acid
- 35

142. (4-Oxo-5-pyridin-2-ylmethylene-2-thioxo-thiazolidin-3-yl)-acetic acid
143. [5-(1-Methyl-1*H*-pyrrol-3-ylmethyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
144. {5-[3-(2-Hydroxy-4,6-dimethoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
145. 3-[5-(4-Benzoyloxy-2-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
146. 3-{5-[3-(5-Benzoyloxy-2-hydroxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
147. 2-{5-[4-(Benzo[1,3]dioxol-5-ylmethoxy)-benzylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-pentanedicarboxylic acid
148. [5-(4-Benzoyloxy-3,5-dihydroxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
149. {5-[3-(2,5-Bis-benzoyloxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
150. 3-[5-(4-Benzoyloxy-3,5-dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
151. 3-[5-(3-Cyclohexyl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
152. 2-{5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-pentanedicarboxylic acid
153. [5-(3,4-Diethoxy-2,5-dimethyl-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
154. {5-[5-(3,4-Diethoxy-2,5-dimethyl-phenyl)-penta-2,4-dienylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
155. [5-(2-Carboxymethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
156. 2-{3-[3-(2-Carboxy-ethyl)-4-oxo-2-thioxo-thiazolidin-5-yliden]-propenyl}-benzoic acid
157. 2-[5-(4-Acetoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
158. Methyl 4-(3-carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-benzoate
159. 4-[3-(3-Carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-yliden)-propenyl]-benzoic acid
160. 3-{4-[3-(2-Carboxy-ethyl)-4-oxo-2-thioxo-thiazolidin-5-ylidenmethyl]-phenyl}-acrylic acid

161. 3-{4-Oxo-5-[3-(4-oxo-4*H*-chromen-3-yl)-allylidene]-2-thioxo-thiazolidin-3-yl}-propionic acid
162. 2-[5-(4-Acetoxy-3,5-dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
- 5 163. 3-(3-Carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-benzoic acid
164. 4-[3-(3-Carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-yliden)-propenyl]-phenyl propionate
165. 3-[5-(5,7-Dimethyl-4-oxo-4*H*-chromen-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
- 10 166. 3-{5-[3-(2-Ethoxycarbonylmethoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
167. 2-[5-(8-Carboxy-naphthalen-1-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
168. [5-(3,4-Diacetoxy-benzyl)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid
- 15 169. {5-[3-(2-Amino-4-oxo-4*H*-chromen-3-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
170. 3-[5-(2-Amino-6,7-dimethyl-4-oxo-4*H*-chromen-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
171. 3-{5-[3-(6-Ethyl-4-oxo-4*H*-chromen-3-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
- 20 172. 2-[5-(6,8-Dimethyl-4-oxo-4*H*-chromen-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-pentanedicarboxylic acid
173. Methyl 2-(3-carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-ylmethyl)-benzoate
174. Methyl 3-[3-(3-carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-yliden)-propenyl]-1*H*-indole-6-carboxylate
- 25 175. 3-{5-[3-(4-Acetoxy-3-methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-propionic acid
176. 3-[4-Oxo-5-(3-phenyl-but-2-enylidene)-2-thioxo-thiazolidin-3-yl]-propionic acid
- 30 177. 2-[4-Oxo-2-thioxo-5-(1-*p*-tolyl-ethylidene)-thiazolidin-3-yl]-pentanedicarboxylic acid
178. {5-[1-(4-Methoxy-phenyl)-ethylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid
179. {5-[1-(3,4-Dichloro-phenyl)-ethyl]-4-oxo-2-thioxo-thiazolidin-3-yl}-acetic acid

180. [4-Oxo-5-(3-thiophen-2-yl-but-2-enylidene)-2-thioxo-thiazolidin-3-yl]-acetic acid
181. 3-[4-Oxo-5-(11-oxo-6,11-dihydro-dibenzo[*b,e*]oxepin-3-ylmethylene)-2-thioxo-thiazolidin-3-yl]-propionic acid
- 5 182. 3-[5-[3-(3,5-Dihydroxy-phenyl)-but-2-enylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid
183. 2-[5-(4-Hydroxy-3-methoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
184. 2-[5-(4-Methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 10 185. 2-(4-Oxo-5-phenthylidene-2-thioxo-thiazolidin-3-yl)-succinic acid
186. 2-[5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
187. 2-[4-Oxo-5-(4-styryl-benzylidene)-2-thioxo-thiazolidin-3-yl]-succinic acid
188. 2-[5-(4-Allyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 15 189. 2-[4-Oxo-5-(4-pyrrolidin-1-yl-benzylidene)-2-thioxo-thiazolidin-3-yl]-succinic acid
190. 2-[5-(3,5-Dihydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
191. 2-[5-[3-(4-Methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 20 192. 2-[4-Oxo-5-(4-propyl-benzylidene)-2-thioxo-thiazolidin-3-yl]-succinic acid
193. 2-[5-(2-Ethoxy-naphthalen-1-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
194. 2-[5-(3-Furan-2-yl-2-methyl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 25 195. 2-[5-[3-(4-Hydroxy-3-methoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
196. 2-[5-[3-(4-*tert*-Butyl-phenyl)-2-methyl-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 30 197. 2-[5-[3-(2-Hydroxy-ethoxy)-benzylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
198. 2-[5-[3-(4-Hydroxy-3,5-dimethoxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
199. 2-[5-(3-Benzo[*b*]thiophen-2-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
- 35

200. 2-[5-(2,4-Bis-benzyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
201. 2-(4-Oxo-5-pyridin-2-ylmethylene-2-thioxo-thiazolidin-3-yl)-succinic acid
202. 2-[5-(4-Benzyloxy-3,5-dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
203. 2-[5-(3-Biphenyl-4-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
204. 2-[5-(3-Carboxy-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
205. 2-[5-(4-Carboxymethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
206. 2-[5-(6-Methyl-4-oxo-4*H*-chromen-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
207. 2-[5-(6-Isopropyl-4-oxo-4*H*-chromen-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid
208. 2-[5-[1-(4-Methoxy-phenyl)-ethylidene]-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid

The following Examples show some process variants which can be used for the synthesis of the compounds in accordance with the invention. However, they are not intended to be a limitation of the object of the invention. The structure of the compounds was proven by <sup>1</sup>H- and, where necessary, by <sup>13</sup>C-NMR spectroscopy. The purity of the substances was determined by C, H, N, P analysis as well as by thin-layer chromatography.

#### Example 1

##### General Process A:

5 mmol of aldehyde of the formula R-CO, wherein R has the significance given above, and 5 mmol of 4-oxo-2-thioxo-thiazolidin-3-ylcarboxylic acid derivative are heated at reflux for 10 hours together with 15 mmol of sodium acetate and 15 ml of glacial acetic acid. After cooling, the mixture is poured into H<sub>2</sub>O. The precipitate is filtered off under suction, rinsed with H<sub>2</sub>O and dried. For purification, it is chromatographed over silica gel with ethyl acetate/heptane (2:1).

The preparation of 2-(4-oxo-2-thioxo-thiazolidin-3-yl)-glutaric acid and 2-(4-oxo-2-thioxo-thiazolidin-3-yl)-succinic acid is effected according to Chem. Heterocycl. Compd. EN 3 528-30 (1967).

- 5    2-(5-Benzo[b]thiophen-2-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-succinic acid  
      (1)

Yellow crystals; m.p. 240°C (dec.)

- 2-(5-Benzo[b]thiophen-2-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-pentanedioic  
10    acid (2)

Yellow crystals; m.p. 220-1°C

- 2-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-3-  
      phenyl-propionic acid (3)

- 15    Yellow crystals; m.p. 160°C (dec.)

- 2-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-3-  
      (1H-indol-3-yl)-propionic acid (4)

Orange crystals; m.p. 140°C (dec.)

- 20    [5-(5-Acetylamino-benzo[b]thiophen-2-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-  
      yl]-acetic acid (5)

Yellow crystals; m.p. >240°C

- 25    5-[3-(4-Methoxy-2,5-dimethyl-phenyl)-allyliden]-4-oxo-2-thioxo-thiazolidin-3-yl-  
      acetic acid (6)

Red crystals; m.p. >240°C

- 5-[3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-  
30    acetic acid (7)

Yellow crystals; m.p. >240°C

- [5-(2,3-Dihydro-benzofuran-5-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic  
      acid (8)

- 35    Yellow crystals; m.p. 246-7°C

(4-Oxo-5-thiophen-2-ylmethylene-2-thioxo-thiazolidin-3-yl)-acetic acid (9)

Yellow crystals; m.p. 237-9°C

5 (5-Benzo[b]thiophen-2-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-acetic acid (10)

Yellow crystals; m.p. 292-4°C

[5-(3-Naphthalen-2-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (11)

Orange crystals; 275-7°C

10

[5-(4-Methoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (12)

Yellow crystals; m.p. 244-6°C

[5-(5-Benzo[b]thiophen-2-yl-penta-2,4-dienylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-  
15 acetic acid (13)

Red crystals; m.p. >240°C

[5-(4-Hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (14)

Yellow crystals; m.p. 230-2°C

20

[5-(4-Methoxy-2,5-dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid  
(15)

Yellow crystals; m.p. 240°C

25 [5-(3-Benzo[b]thiophen-2-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid  
(16)

Orange crystals; m.p. >240°C

[5-(4-Methoxy-3-methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid  
30 (17)

Yellow crystals; m.p. 235-6°C

2-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-  
pentanedioic acid (18)

35 Yellow crystals; m.p. 130°C (dec.)



[5-(4-Benzoyloxy-3,5-dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (19)

M.p. 128-30°C

5

[5-(3,4-Bis-benzoyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (20)

Yellow crystals; m.p. 187-8°C

[5-(3-Biphenyl-4-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (21)

10 Orange crystals; m.p. 130°C (dec.)

5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (22)

Brown crystals; m.p. 100°C (dec.)

15

[5-(3-tert-Butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (23)

Yellow crystals; m.p. >240°C

20 2-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-succinic acid (24)

Brown crystals; m.p. 240°C (dec.)

[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (25)

25

Orange crystals; m.p. 120-1°C

[5-(4-Benzoyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (26)

Yellow crystals; m.p. 205-6°C

30

5-[1-(3,5-Dihydroxy-phenyl)-ethylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (27)

Yellow crystals; m.p. 184-8°C

5-[1-(4-Carboxymethoxy-phenyl)-ethylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (28)

Yellow crystals; m.p. 111-20°C (dec.)

5 [4-Oxo-2-thioxo-5-(2,3,4-trihydroxy-benzylidene)-thiazolidin-3-yl]-acetic acid (29)

Ochre-coloured crystals; m.p. 263°C (dec.)

[5-(2-Hydroxy-4,6-dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (30)

10 Pale brown crystals; m.p. 194°C (dec.)

[5-(3-Benzoyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (31)

Yellow crystals; m.p. 178-81°C

15 3-[5-(4-Benzoyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid (32)

Yellow crystals; m.p. 188-91°C

2-[5-(4-Benzoyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid (33)

Yellow crystals; m.p. 125-8°C

20

[5-(5-Benzoyloxy-2-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (34)

Orange crystals; m.p. 130-3°C

25 5-[4-(4-Methoxy-benzoyloxy)-benzylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (35)

Yellow crystals; m.p. 172-3°C

30 5-[4-(Benzo[1,3]dioxol-5-ylmethoxy)-benzylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (36)

Yellow crystals; m.p. 206-7°C

5-[4-Oxo-2-thioxo-5-(3,4,5-trihydroxy-benzylidene)-thiazolidin-3-yl]-pentanecarboxylic acid (37)

35 m.p. 212-4°C

5-[4-(3-Methoxy-benzyloxy)-benzylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid  
(38)

Yellow crystals; m.p. 191-3°C

5

[5-(4-Hydroxy-3,5-dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid  
(39)

Orange crystals; m.p. 277-9°C

10 [5-(4-Benzyloxy-3,5-dihydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic  
acid (40)

M.p. 178-80°C

[5-(2,5-Bis-benzyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (41)

15 Yellow crystals; m.p. 196-8°C

[4-Oxo-2-thioxo-5-(3,4,5-triacetoxy-benzylidene)-thiazolidin-3-yl]-acetic acid (42)

Orange crystals; m.p. 200°C (dec.)

20 5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-  
yl-acetic acid (43)

Red crystals; m.p. 252-3°C

(5-Cyclohex-3-enylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-acetic acid (44)

25 Beige crystals; m.p. 180-2°C

[4-Oxo-5-(3-phenyl-propylidene)-2-thioxo-thiazolidin-3-yl]-acetic acid (45)

Orange crystals; m.p. 108-11°C

30 5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienyliden]-4-oxo-2-  
thioxo-thiazolidin-3-yl-acetic acid (46)

Orange crystals; m.p. 153-5°C

5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-3-methyl-2-thioxo-thiazolidin-4-one (47)

35 Yellow crystals; m.p. >240°C

Methyl [5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetate (48)

Yellow crystals; m.p. 165-70°C

5

2-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-N,N-diethyl-acetamide (49)

Yellow crystals; m.p. 223-5°C

10 Methyl 5-[3-(5,6-diethoxy-benzo[b]thiophen-2-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetate (50)

Violet crystals; m.p. 211-5°C

15 2-5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-N,N-diethyl-acetamide (51)

Red crystals; m.p. 210-2°C

Benzyl 4-(3-carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-piperidine-1-carboxylate (52)

20 Yellow crystals; m.p. 114-5°C

5-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (53)

Black (sic) crystals; m.p. 144°C (dec.)

25

[5-(3,4-Dihydroxy-2,5-dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (54)

Yellow crystals; m.p. >240°C

30 [5-(3,4-Diethoxy-2,5-dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (55)

Ochre coloured crystals; m.p. 185-90°C

5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (56)

Green crystals; m.p. 210°C (dec.)

5 5-[5-Methyl-7-(2,6,6-trimethyl-cyclohex-1-enyl)-hepta-2,4,6-trienyliden]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid (57)

Black crystals; m.p. 192-5°C

10 3-(5-Benzo[1,3]dioxol-5-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-propionic acid (58)

Yellow crystals; m.p. 174-6°C

3-[4-Oxo-2-thioxo-5-(2,6,6-trimethyl-cyclohex-1-enylmethylene)-thiazolidin-3-yl]-propionic acid (59)

15 Yellow-orange crystals; m.p. 166-8°C

3-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid (60)

Yellow crystals; m.p. 218-9°C

20

3-(5-Naphthalen-1-ylmethylene-4-oxo-2-thioxo-thiazolidin-3-yl)-propionic acid (61)

Orange crystals; m.p. 159-61°C

25 3-[5-(3-Benzo[b]thiophen-2-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid (62)

Orange crystals; m.p. 246-8°C

[5-(4-Dibutylamino-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (63)

Orange crystals; m.p. 186-8°C

30

[4-Oxo-5-(4-pentyl-benzylidene)-2-thioxo-thiazolidin-3-yl]-acetic acid (64)

Yellow crystals; m.p. 160-2°C

[5-(3-Methoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (65)

Yellow crystals; m.p. 193-6°C

[4-Oxo-2-thioxo-5-(2,4,5-trimethyl-benzylidene)-thiazolidin-3-yl]-acetic acid (66)

5 Yellow crystals; m.p. 234-6°C

[5-(2-Hexyloxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (67)

Yellow crystals; m.p. 148-50°C

10 [5-(4-Methyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (68)

Yellow crystals; m.p. 234-6°C

[5-(4-Methoxy-2,3-dimethyl-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (69)

15 Yellow crystals; m.p. 215-7°C

[5-(4-Hydroxy-3,5-dimethoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (70)

Orange crystals; m.p. 238-40°C

20

5-(3-Carboxymethyl-4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-2-hydroxy-benzoic acid (71)

Yellow crystals; m.p. >260°C

25 3-5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-propionic acid (72)

Orange crystals; m.p. 160-1°C

30 [5-(1,4-Dihydroxy-10-methoxy-5,8-dimethyl-3,7-dioxo-1,3-dihydro-7H-benzo[e]furo[3',4':3,4]benzo[b][1,4]dioxepin-11-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (73)

Dark green crystals; m.p. >260°C

[5-(2-Methyl-1H-indol-3-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid  
(74)

Brown crystals; m.p. 268-70°C

5 [5-(3,4-Diacetoxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (75)

Yellow crystals; m.p. 193-5°C

#### Example 2

- 10 Compounds of general formula (I) were investigated in a suitable assay for the capability of stimulating cyclic adenylate cyclase.

Table I:

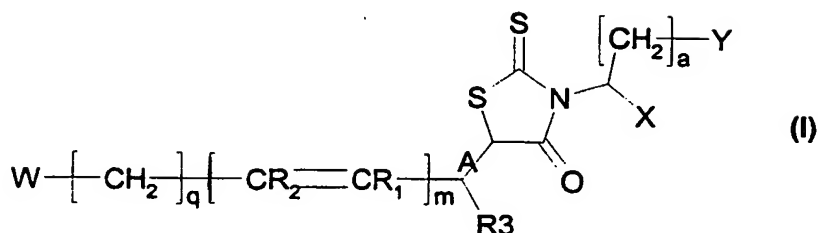
Example No.	Name	% cAMP (Test conc. 50μM)
<u>3</u>	2-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-3-phenyl-propionic acid	8
<u>13</u>	[5-(5-Benzo[b]thiophen-2-yl-penta-2,4-dienylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid	10
<u>16</u>	[5-(3-Benzo[b]thiophen-2-yl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid	8
<u>22</u>	5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid	10
<u>23</u>	[5-(3-tert-Butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid	8
<u>25</u>	[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid	40
<u>46</u>	5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-acetic acid	30
<u>59</u>	3-[4-Oxo-2-thioxo-5-(2,6,6-trimethyl-cyclohex-1-enylmethylene)-thiazolidin-3-yl]-propionic acid	15
<u>60</u>	3-[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-propionic acid	20
<u>72</u>	3-5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-4-oxo-2-thioxo-thiazolidin-3-yl-propionic acid	15



## Patent Claims

1. Use of compounds of general formula (I)

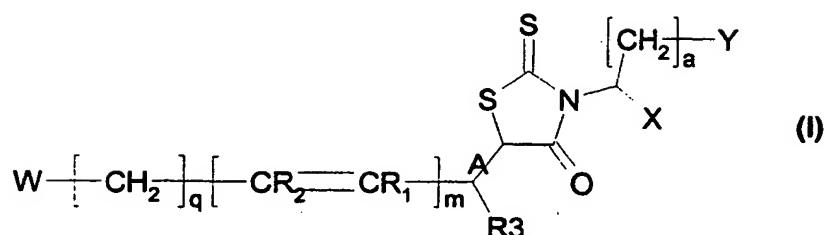
5



in which

- 10 m signifies a number between 0-8,  
 q signifies a number between 0-8  
 a signifies a number between 0-4  
 A signifies a single or double bond  
 R<sub>1</sub>, R<sub>2</sub> signify hydrogen or lower alkyl, whereby  
 15 R<sub>1</sub> and R<sub>2</sub> can be the same or different and, when m signifies 2-8, R<sub>1</sub> and R<sub>2</sub> in  
 the group CR<sub>1</sub>=CR<sub>2</sub> can have various significances within the following sequence  
 R<sub>3</sub> signifies hydrogen or lower alkyl  
 X signifies hydrogen or -(CH<sub>2</sub>)<sub>b</sub>-COR<sub>4</sub> with b = 0-4  
 Y signifies hydroxyl, -COR<sub>4</sub>, phenyl or indolyl residue  
 20 R<sub>4</sub> signifies hydroxyl, lower alkoxy or the NR<sub>1</sub>R<sub>2</sub> residue, whereby R<sub>1</sub> and R<sub>2</sub> can be  
 the same or different  
 W signifies an optionally mono- or polysubstituted saturated or unsaturated  
 mono-, bi- or tricycle which can contain one or more hetero atoms,  
 25 for the preparation of medicaments for the treatment and prevention of metabolic bone  
 disorders,

## 2. Compounds of general formula (I)



5

in which

m signifies a number between 0-8,

q signifies a number between 0-8

a signifies a number between 0-4

10 A signifies a single or double bond

R<sub>1</sub>, R<sub>2</sub> signify hydrogen or lower alkyl, whereby

R<sub>1</sub> and R<sub>2</sub> can be the same or different and, when m signifies 2-8, R<sub>1</sub> and R<sub>2</sub> in the group CR<sub>1</sub>=CR<sub>2</sub> can have various significances within the following sequence

R<sub>3</sub> signifies hydrogen or lower alkyl15 X signifies hydrogen or -(CH<sub>2</sub>)<sub>b</sub>-COR<sub>4</sub> with b = 0-4Y signifies hydroxyl, -COR<sub>4</sub>, phenyl or indolyl residueR<sub>4</sub> signifies hydroxyl, lower alkoxy or the NR<sub>1</sub>R<sub>2</sub> residue, whereby R<sub>1</sub> and R<sub>2</sub> can be the same or different

W signifies an optionally mono- or polysubstituted saturated or unsaturated  
20 mono-, bi- or tricycle which can contain one or more hetero atoms,

whereas W is not phenyl or indolyl, if m and g are both 0, R<sub>3</sub>, is hydrogen and A is a double bond,

25 as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I)

3. Medicament containing at least one compound of general formula (I) according  
30 to claim 2 in admixture with usual pharmaceutical adjuvants and carrier material

**PCT/EP 99/07248**

IPC 7 C07D277/36 C07D417/06 C07D493/04 A61K31/425  
 //(C07D493/04.321:00.307:00)

According to International Patent Classification (IPC) or to both national classification and IPC

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

### **G. DOCUMENTS CONSIDERED TO BE RELEVANT**

## INTERNATIONAL SEARCH REPORT

Application No

PCT/EP 99/07248

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 391 644 A (ELI LILLY AND COMPANY) 10 October 1990 (1990-10-10) claims	1,2
X	EP 0 343 643 A (WARNER LAMBERT COMPANY) 29 November 1989 (1989-11-29) claims	1,2
X	EP 0 047 109 A (ONO PHARMACEUTICAL CO., LTD) 10 March 1982 (1982-03-10) claims	1,2
X	EP 0 045 165 A (ONO PHARMACEUTICAL CO., LTD) 3 February 1982 (1982-02-03) claims	1,2
Y	US 5 143 927 A (BOSCHELLI DIANE H ET AL) 1 September 1992 (1992-09-01) column 3, line 66 -column 4, line 50; example 4	1-3
Y	US 5 143 929 A (BELLIOTTI THOMAS R ET AL) 1 September 1992 (1992-09-01) column 4; claims	1-3
Y	US 5 747 517 A (PANETTA JILL A. ET AL) 5 May 1998 (1998-05-05) claims	1-3
Y	WO 98 01445 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15) claims	1-3
Y	DE 43 18 550 A (BOEHRINGER MANNHEIM) 8 December 1994 (1994-12-08) claims	1-3
Y	EP 0 677 517 A (ELI LILLY AND COMPANY) 18 October 1995 (1995-10-18) claims	1-3
Y	EP 0 237 138 A (YAMANOUCHI PHARMACEUTICAL CO. LTD) 16 September 1987 (1987-09-16) claims	1-3
A	EP 0 425 109 A (PFIZER INC.) 2 May 1991 (1991-05-02) the whole document	1-3

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07248

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9626207	A	29-08-1996	AU 4731196 A JP 9235284 A ZA 9601478 A	11-09-1996 09-09-1997 28-08-1996
EP 0587377	A	16-03-1994	AU 676843 B AU 4621893 A CA 2105598 A CN 1091006 A CZ 9301814 A EP 0915090 A FI 933946 A HU 70184 A IL 106877 A IL 119119 A JP 6192091 A MX 9305444 A NO 933198 A NO 981911 A NZ 248573 A PL 300335 A US 5523314 A US 5716975 A US 5661168 A ZA 9306492 A	27-03-1997 17-03-1994 11-03-1994 24-08-1994 16-03-1994 12-05-1999 11-03-1994 28-09-1995 10-03-1998 16-08-1998 12-07-1994 31-05-1994 11-03-1994 11-03-1994 27-02-1996 21-03-1994 04-06-1996 10-02-1998 26-08-1997 02-03-1995
EP 0434394	A	26-06-1991	AT 169294 T AU 639734 B AU 6826690 A CA 2032330 A CN 1052668 A, B DE 69032537 D DE 69032537 T ES 2121748 T FI 906273 A HU 216732 B IL 96654 A IL 108962 A JP 4279573 A MX 23803 A NO 300458 B NZ 236472 A PT 96198 A, B RU 2036915 C RU 2050355 C US 5387690 A US 5216002 A	15-08-1998 05-08-1993 27-06-1991 22-06-1991 03-07-1991 10-09-1998 21-01-1999 16-12-1998 22-06-1991 30-08-1999 29-06-1995 05-12-1996 05-10-1992 28-02-1994 02-06-1997 26-03-1993 30-09-1991 09-06-1995 20-12-1995 07-02-1995 01-06-1993
EP 291007	A	17-11-1988	AU 1558288 A DK 247788 A JP 1052766 A JP 2608097 B	17-11-1988 12-11-1988 28-02-1989 07-05-1997
EP 0391644	A	10-10-1990	AT 139531 T AU 629322 B AU 5293490 A CA 2013599 A DE 69027472 D DE 69027472 T	15-07-1996 01-10-1992 11-10-1990 07-10-1990 25-07-1996 05-12-1996

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 99/07248

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0391644 A		DK 391644 T	15-07-1996
		ES 2088965 T	01-10-1996
		GR 3020500 T	31-10-1996
		JP 2290862 A	30-11-1990
		US 5356917 A	18-10-1994
		US 5691367 A	25-11-1997
EP 0343643 A	29-11-1989	AT 103175 T	15-04-1994
		AU 626863 B	13-08-1992
		AU 3505889 A	30-11-1989
		CA 1340247 A	15-12-1998
		DE 68914029 D	28-04-1994
		DE 68914029 T	07-07-1994
		DK 252089 A	26-11-1989
		EP 0565135 A	13-10-1993
		ES 2063073 T	01-01-1995
		FI 892522 A	26-11-1989
		IE 62214 B	11-01-1995
		JP 2062864 A	02-03-1990
		JP 2899309 B	02-06-1999
		KR 9702228 B	26-02-1997
		NO 892083 A	27-11-1989
		NZ 229266 A	23-12-1991
		PH 27092 A	26-02-1993
		PT 90662 A, B	30-11-1989
		US 5464856 A	07-11-1995
		US 5208250 A	04-05-1993
		US 5306822 A	26-04-1994
EP 0047109 A	10-03-1982	JP 1442337 C	08-06-1988
		JP 57040478 A	06-03-1982
		JP 62051955 B	02-11-1987
		US 4831045 A	16-05-1989
		US 4791126 A	13-12-1988
		US 4464382 A	07-08-1984
EP 0045165 A	03-02-1982	JP 1446394 C	30-06-1988
		JP 57028074 A	15-02-1982
		JP 62057186 B	30-11-1987
		US 4446143 A	01-05-1984
US 5143927 A	01-09-1992	US 5250552 A	05-10-1993
US 5143929 A	01-09-1992	NONE	
US 5747517 A	05-05-1998	CA 2144385 A	17-09-1995
		EP 0677517 A	18-10-1995
		JP 7258235 A	09-10-1995
WO 9801445 A	15-01-1998	EP 0912560 A	06-05-1999
		US 5985905 A	16-11-1999
DE 4318550 A	08-12-1994	AU 6998394 A	03-01-1995
		WO 9429287 A	22-12-1994
EP 0677517 A	18-10-1995	CA 2144385 A	17-09-1995
		JP 7258235 A	09-10-1995
		US 5747517 A	05-05-1998

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07248

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0237138	A	16-09-1987	AU 6740187 A	09-07-1987
			DK 4487 A	08-07-1987
			JP 63165368 A	08-07-1988
EP 0425109	A	02-05-1991	AT 109349 T	15-08-1994
			AU 624739 B	18-06-1992
			AU 6458290 A	18-04-1991
			CA 2027394 A,C	14-04-1991
			DE 69011272 D	08-09-1994
			DE 69011272 T	24-11-1994
			DK 425109 T	21-11-1994
			HU 9500128 A	28-07-1995
			IE 63140 B	22-03-1995
			IL 95880 A	31-12-1995
			JP 1949833 C	10-07-1995
			JP 3133929 A	07-06-1991
			JP 6084300 B	26-10-1994
			NZ 235638 A	24-02-1997
			PT 95566 A,B	14-08-1991
			US 5192790 A	09-03-1993

**This Page Blank (uspto)**